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Does Mesalazine improve the symptoms of patients with irritable bowel syndrome (IBS)?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine – Georgia Campus
Suwanee, Georgia

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ABSTRACT

OBJECTIVE: The purpose of this EBM review is to determine, “Does Mesalazine improve the symptoms of patients with irritable bowel syndrome (IBS)?”.

STUDY DESIGN: Review of three English language primary studies, published between 2011 and 2016.

DATA SOURCES: Three randomized controlled trials (RCTs) were found through the Cochrane Library, Embase, and PubMed. These studies analyzed the effectiveness of Mesalazine in treating the symptoms of patients with IBS.

OUTCOMES MEASURED: The outcomes measured included relief of abdominal pain (primary outcome) and abdominal pain intensity. The outcomes were measured by a binary scale (“yes” or “no” or relief of pain, pain severity scale rated on a scale of 1-10, and an abdominal pain score/scale of 0-10. P-values were used to assess the significance of these outcomes in two studies, and NNT (number needed to treat), RBI (relative benefit increase), and ABI (absolute benefit increase) were used to assess the significance of these outcomes in one study.

RESULTS: The results from the studies show conflicting evidence, as two studies showed no statistically significant difference in the relief of abdominal pain/pain intensity between Mesalazine and Placebo treatment. However, one study did support the question that Mesalazine had a greater effect on treating abdominal pain than the standard treatment for IBS.

CONCLUSION: Based upon the evidence and results shown in the three studies reviewed, the use of Mesalazine in treating the primary symptom of IBS, abdominal pain, cannot be justified as a statistically significant treatment. Barbara and Lam both showed that Mesalazine did not have a statistically significant effect on the relief of abdominal pain or lowered abdominal pain intensity post-treatment, while Dorofeyev did show that Mesalazine was superior to standard therapy without Mesalazine. Thus, further investigation should be carried out to determine if Mesalazine is truly effective at improving the main symptom of abdominal pain in IBS patients.

KEY WORDS: Irritable Bowel Syndrome, Mesalazine

INTRODUCTION

Irritable Bowel Syndrome, or IBS, is a condition of the gastrointestinal tract that is characterized primarily by “chronic abdominal pain and altered bowel habits”.¹ This topic of medicine is relevant to the practice of Physician Assistants due to the high prevalence of the disease. In fact, it is estimated that 10-20% of the North American population is affected by IBS, so it is an extremely relevant condition to be familiar with as a practicing PA.¹ In addition to the high percentage of the North American population affected by IBS, “25-50% of all gastroenterologist referrals” involve IBS.⁴

In addition to the high prevalence of the disease, there are significant direct medical costs that can be attributed to IBS. In the United States, it is estimated to be around \$1.6–\$10.5 billion per year.^{5,6,7} IBS also accounts for an astounding number of healthcare visits, where the disease accounted for 1.6 million ambulatory care visits in 2009 and 280,000 hospitalizations in 2010.^{8,9}

While the exact pathophysiology of IBS is unknown, there are several proposed factors that may play into the mechanisms of the condition, such as “altered gastrointestinal motility, visceral hypersensitivity, post infectious reactivity, alteration in fecal micro flora, bacterial overgrowth, food sensitivity, carbohydrate malabsorption, and intestinal inflammation”.¹²

In addition to the multiple proposed etiologies of the disease, there are a myriad of different methods used to treat IBS. They initially include reassurance, education, diet modifications, and increased physical activity.¹² There are other pharmacologic agents, such as laxatives for constipation symptoms, anti-diarrheal agents for diarrhea symptoms, bile acid sequestrants for diarrhea symptoms, and antispasmodics such as Dicyclomine.^{12,14} In addition, antidepressants, such as tricyclic antidepressants, have shown positive analgesic effects in

patients with IBS.¹³ In patients that have not responded to the above treatments, a short trial of antibiotics, such as Rifaximin, may be prescribed.¹⁵

While these treatments have the potential to relieve common symptoms of IBS and help patients to live a symptom-free life, each patient responds to treatments differently, and some patients may not respond completely to multiple different treatments. Therefore, different treatment methods have been sought out by researchers. One such treatment method is Mesalazine, which is widely known to be a common treatment for IBD patients. Because one of the proposed factors contributing to the pathophysiology of IBS is intestinal inflammation, it has been proposed by some researchers that anti-inflammatory medications, such as Mesalazine, may prove to be effective.³

OBJECTIVE

The purpose of this EBM review is to determine “Does Mesalazine improve the symptoms of patients with irritable bowel syndrome (IBS)?”.

METHODS

There were several criterion used in the selection of studies. The populations in these studies included both male and female patients that met the Rome III criteria for an IBS diagnosis,¹¹ and that were greater than eighteen years of age. Each of the studies used in this review used Mesalazine as an intervention for measuring patients’ IBS symptoms resolving with treatment. These interventions included 800mg PO 3 x daily for 12 weeks, followed for an additional 12 weeks,¹ 500 mg Mesalazine 4 x daily for 28 days,² and 2 grams Mesalazine PO twice daily for 3 months.³ These interventions were compared to placebo PO 3 x daily for 12 weeks,¹ standard therapy without Mesalazine for 28 days,² and 2 g placebo PO once daily for one week, and if tolerated, then 2 g twice a day for 11 weeks,³ respectively. The primary outcome

that is being addressed is the relief of the IBS symptom of abdominal pain. This outcome was measured by a binary scale,¹ and various pain severity score scales.^{2,3} The types of studies included in this review included a phase III, Multicenter, Tertiary setting, Parallel-Arm, Randomized, Double-Blind, Placebo-Controlled Trial,¹ a controlled, randomized, blind clinical trial,² and a multicenter, two-arm, parallel-group, double-blind, randomized placebo-controlled trial.³

The author used the keywords “Mesalazine”, “Mesalamine”, “Irritable Bowel Syndrome”, and “IBS” to carry out a detailed search of different studies. The detailed search included searching through the Cochrane Library, Embase, and PubMed. All articles that were selected for use in this review were based on relevance and that the outcomes of the studies were patient-oriented outcomes (POEMs). All articles selected were published in English, and all articles selected were published in peer-reviewed journals. Inclusion criteria included studies that were RCTs published after 2001, and exclusion criteria included studies with patients under the age of 18 or studies that included patients that did not fit the criteria of an IBS diagnosis. The statistics reported in these articles included p-values, where a p-value < 0.05 was considered statistically significant, and one article included information to calculate the number needed to treat (NNT), relative benefit increase (RBI), and absolute benefit increase (ABI). A detailed listing of the characteristics of the included studies is listed in Table 1 below.

Table 1 - Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Barbara (2016) ¹	Parallel-Arm, Randomized, Double-Blind, Placebo-	180	18 - 65	Positive diagnosis of all IBS subtypes and negative colonoscopy or barium enema examination within the previous 5 years or negative relevant	Pts. that were pregnant, currently used NSAIDs, steroids, or mast cell stabilizers, current use of antibiotics, treatment with lactulose, pts. with a	50	Mesalazine, 800 mg, 3 x daily for 12 weeks and followed for an additional 12 weeks

	Controlle d Trial			additional screening or consultation.	history of abdominal surgery, history of IBD or celiac disease, pts. with asthma, or patients with psychiatric disorders.		
Dorofe yev (2011) ²	Controlle d, randomiz ed, blind clinical trial	360	18 - 65	Diagnosis of IBS according to Rome III criteria, absence of any bowel infection, or post-infectious IBS.	Pts. with specific alarm symptoms such as first symptoms \geq 50 years, loss of weight, blood in stool, fever, or cancer anamnesis in relatives	0	500 mg Mesalazine 4 x daily for 28 days
Lam (2016) ³	Multicen ter, two- arm, parallel- group, double- blind, randomiz ed placebo- controlle d trial	136	18 - 75	Diagnosis of IBS- D according to modified Rome III criteria, normal colonoscopy, normal blood count, serum calcium and albumin, C-reactive protein and negative test for Celiac and lactose intolerance, among others listed in article.	Pregnancy, prior history of major abdominal surgery, liver or kidney impairment or chronic ingestion of any anti- inflammatory drugs or medications that could affect drug motility.	16	2 grams Mesalazine PO twice daily for 3 months

OUTCOMES MEASURED

The primary outcome that is being addressed in this review the relief of the symptom of abdominal pain, which is considered a POEM. This outcome should help to answer the question “Does Mesalazine improve the symptoms of patients with irritable bowel syndrome (IBS)?”, as abdominal pain is a key feature of the disease. With the first article, authored by Barbara et al, the primary efficacy endpoint was satisfactory relief of abdominal pain/discomfort for at least half of the weeks of the treatment period.¹ The primary endpoint was assessed using a binary scale based on the patients’ answers to the following weekly question: “Did you have satisfactory relief of your abdominal discomfort or pain during the last week?”¹. The patients were classified as responders if they reported an affirmative answer in at least 50% of weeks over a 3-month treatment period (50% rule).¹

The primary outcome that Dorofeyev et al measured was the parameter of pain intensity.² Before and after treatment, patients characterized their pain intensity by a visual analog scale (a score of zero meant no pain and a score of 10 equaled the worst imaginable pain).²

Finally, one of the outcomes measured in the Lam et al study was abdominal pain severity while on the Mesalazine or the Placebo treatment during the study. For this outcome, patients completed 7-day weekly stool diaries for 12 weeks. Patients scored their abdominal pain severity between 0 (no symptoms) and 10 (extremely severe symptoms).³

RESULTS

All three studies that are evaluated in this review are randomized controlled trials that included an assessment of the satisfactory relief of abdominal pain/IBS symptoms and pain intensity. The population included in all three studies were adults over the age of 18. The comparisons in two of the studies was a placebo pill,^{1,3} and one study's intervention was compared to "standard therapy without Mesalazine for 28 days".² The study conducted by Barbara et al contained dichotomous data that could be used to calculate RBI, ABI, and NNT,¹ while the other two studies included in this review contained continuous data that could not be converted, and rather, used p-values to determine the statistical significance between the interventions and comparisons.^{2,3}

The study conducted by Barbara et al included 180 patients that were aged 18-65 years old, and 50 of those participants withdrew from the study. These participants withdrew for several reasons, including "consent withdrawal (17 patients), adverse events (14 patients), lost during follow-up (8 patients), protocol violation (6 patients), and other reasons (5 patients)".¹ Compliance of study treatment completion was between 70% and 120%, though the study did

not mention how this was measured.¹ After patients went through the screening process in order to become enrolled in the study, the patients were assigned randomly to the intervention or control group (Mesalazine 800 mg PO 3x daily for 12 weeks or Placebo PO 3x daily for 12 weeks, respectively). 88 patients were randomized to Mesalazine, while 92 were randomized to the Placebo group. The study's inclusion and exclusion criteria can be found in Table 1. The primary efficacy endpoint in this study was satisfactory relief of abdominal pain/discomfort for at least half of the weeks of the treatment period, and this was measured by using a binary scale based on the patients' answers to the following weekly question: "Did you have satisfactory relief of your abdominal discomfort or pain during the last week?".¹ The patients were classified as responders if they reported an affirmative answer in at least 50% of weeks over a 3-month treatment period (50% rule).¹ Analysis was performed by intention-to-treat.

The data from the study was considered dichotomous data. It was found that 68.6% of the patients in the Mesalazine group were responders, while 67.4% of Placebo group patients were responders.¹ The relative benefit increase (RBI) was found to be 0.018, or 1.8%, and the absolute benefit increase (ABI) was found to be 0.012, or 1.2%. This showed that the number needed to treat (NNT) was 84, therefore, 84 patients needed to be treated with Mesalazine in order to achieve one positive outcome from the treatment. These evaluations are highlighted in Table 2. The study highlighted several adverse and serious adverse events with treatment during the study, where the Placebo group patients featured zero serious adverse events, while the Mesalazine group patients featured four serious adverse events (two cases of gastroenteritis, one case of ischemic colitis, and one case of breast cancer).¹ The placebo group featured 38 adverse events (such as URIs, diarrhea, headaches, nausea, and vomiting), while the Mesalazine group featured 31 adverse events.¹

Table 2: Results of Satisfactory Relief of Abdominal Pain in Barbara et al¹

RBI	ABI	NNT
0.018	0.012	84

The study conducted by Dorofeyev et al included 360 patients from the ages of 18-65 years old. Zero patients withdrew from the study, which shows that all subjects who entered the trial were accounted for and attributed to at its conclusion. After patients were screened for entrance into the study, patients were randomized into two groups. Every third patient was assigned to the treatment group and received Mesalazine 500mg PO QID x 28 days; thus, 120 patients were in the treatment group. The control group contained the remaining 240 patients, and these participants received “standard treatment without mesalazine”.² The standard treatment included Loperamide (2-4mg PO PRN) for diarrhea, Plantago ovata 3.25 g BID or lactulose syrup 15-20 mL BID for constipation, Mebeverine 400 mg QD for abdominal pain, or Simethicon x 3-5 days for meteorism.² The study’s inclusion and exclusion criteria can be found in Table 1. The outcome from this study that is being addressed is abdominal pain intensity. Before and after treatment, patients characterized their pain intensity by a visual analog scale (0 = no pain and 10 = worst imaginable pain).² Analysis was performed by intention to treat (ITT).

The data from this study was considered to be continuous data. For the intention to treat population, the baseline mean pain intensity score for all patients (patients in both the intervention and control groups) together = 7.6 (n = 360). For the intention to treat population for the control group, mean pain intensity score after the study was 3.8 (n = 240). For the intention to treat population for the Mesalazine treatment group, the mean pain intensity score after the study was 1.4 (n = 120).² Table 3 lists the mean pain intensity scores for the intention to treat population. Significance of differences of mean values between the mesalazine and standard treatment groups was determined by Student’s t-test. The article did not specifically state the p-

value for the difference in mean abdominal pain intensity score after treatment for the intention to treat population, but did indicate that the difference between the two groups in the intention-to-treat population was statistically significant, with a p-value < 0.05 . The percent mean change from baseline was not calculated by the experimenters, and could not be interpreted, due to the study only listing the baseline mean pain intensity score for all participants together, and then separating the final pain intensity score based on intervention or control group. Study compliance regarding patient adherence was not discussed in the study. The study did assess safety and adverse events with regards to its study participants. Thirteen patients that were in the Mesalazine group reported an adverse event and twenty-nine patients that were in the standard treatment group reported adverse events, which consisted of “headaches, nasopharyngitis, and flu-like infections”.² There were no significant adverse events reported in the study.

Table 3: Mean Abdominal Pain Intensity Scores for ITT Population in Dorofeyev et al²

	Baseline Mean Pain Intensity Score for all Study Participants	Mean Pain Intensity Score Post-Treatment for Mesalazine Group	Mean Pain Intensity Score Post-Treatment for Standard Treatment Group
Pain Intensity Score (1-10)	7.6	1.4	2.8

The study conducted by Lam et al included 136 participants from the ages of 18-75 years old. Inclusion and exclusion criteria is listed in Table 1. These 136 patients were randomly allocated to either the Mesalazine or Placebo treatment group, where 2 grams Mesalazine PO twice daily for 3 months was used for the intervention, and 2 g placebo PO once daily for one week, and if tolerated, then 2 g twice a day for 11 weeks, was used for the control group.³ In the Mesalazine group, two patients withdrew consent, one was lost to follow-up, and eight had an adverse event, so only 57 patients were included in the ITT analysis.³ For the control group, two patients withdrew consent, one was lost to follow up, one had an incomplete diary, and six had

adverse events, so only 58 patients were included in the ITT analysis. The outcome that is being addressed from this study is daily mean abdominal pain score, where participants used a daily stool diary and rated abdominal pain daily on a score from 0 (no symptoms) to 10 (extremely severe abdominal pain).³

The baseline daily mean abdominal pain score for the Mesalazine group, that included the patients that later withdrew from the study, was 4.1, with a standard deviation (SD) of 2.2. The baseline daily mean abdominal pain score for the placebo group, that included the patients that later withdrew from the study, was 3.6, with a SD of 2.0. At the end of treatment (EOT), the average abdominal pain score for the Mesalazine group was 2.8, with a SD of 2.1. The average abdominal pain score for the placebo group at EOT was 2.2, with a SD of 2.1. The between group comparison at EOT, with a 95% CI, was 0.07, and when analyzed according to the Consolidated Standards of Reporting Trials guidance, using Stata V.13. showed a p-value of 0.83,³ which is not statistically significant ($p < 0.05$ is considered statistically significant). These values can be found listed in Table 4. Compliance was measured in the study as taking greater than or equal to 75% of the medication throughout the twelve weeks of the study. The amount of medication taken was determined by the number of pills remaining the medication boxes returned at EOT. Compliance with medication during the whole twelve weeks of the study for the ITT population was 71% for Mesalazine and 72% for the placebo groups.³ Adverse events were recorded during the study and all patients that reported these adverse events were not included in the ITT population, which included symptoms such as bloating, chest pain, dizziness, rash, and others. Two patients from the Mesalazine group and three patients from the placebo group reported exacerbation of IBS symptoms (worsening abdominal pain or diarrhea).³ The only major adverse event was that one patient in the Mesalazine group was found to have breast

cancer. Overall, there were eight adverse events in the Mesalazine group, and six adverse events in the placebo group.³

Table 4: Average Abdominal Pain Score with Standard Deviation in Lam et al study³

	Mesalazine Baseline	Placebo Baseline	Mesalazine EOT	Placebo EOT
Mean Abdominal Pain Score	4.1	3.6	2.8	2.2
Standard Deviation	2.2	2.0	2.1	2.1

DISCUSSION

The three randomized controlled trials discussed in this study were created to investigate whether Mesalazine is an effective treatment for relieving the symptoms, primarily abdominal pain, in IBS patients. The results from the studies show conflicting evidence, as Barbara et al and Lam et al show no statistically significant difference in the relief of abdominal pain/pain intensity between Mesalazine and Placebo treatment, while Dorofeyev et al did show a statistically significant difference between Mesalazine and standard treatment for IBS patients. While this review is primarily reviewing the effect Mesalazine has on the relief of the symptom of abdominal pain, there are many other symptoms of IBS, such as bloating and stool frequency,^{1,3} as well as biopsy samples, that the studies also investigated that can be reviewed and analyzed.

There were several limitations to these studies. For instance, with the pain severity scales used in Dorofeyev et al and Lam et al, these were a subjective measure, as different people have different pain tolerances and these results of abdominal pain intensity post treatment could not be considered as consistent across all patients. In addition, the Dorofeyev et al study did not compare baseline mean pain intensity scores separately for Mesalazine and standard treatment; thus, the analysis of the percent mean change from baseline cannot accurately be calculated.

While the experimenters in this study did record a statistically significant difference in the intervention and control group treatments post-treatment, they did not compare the post-treatment to the baseline. The Dorofeyev article also did not use a standard placebo for the control, and only conducted their study for four weeks.

The primary use of Mesalazine and other aminosalicylates is for the treatment of inflammatory bowel disease. It has been in use for more than 30 years in the treatment of IBD, more specifically now in Ulcerative Colitis treatment, and has the best safety profile of all IBD drugs.¹⁰ Mesalazine side effects are minor in nature and include headache, nausea, and diarrhea. More serious side effects include pancreatitis and renal dysfunction, but are rarer, and warrant further investigation.¹⁰

CONCLUSION

This review shows inconsistent and inconclusive evidence for the use of Mesalazine in improving the symptoms in IBS patients, namely abdominal pain. Two studies showed no statistically significant evidence between Mesalazine and placebo, while one study suggested there was a significant difference in the abdominal pain intensity between Mesalazine and standard treatment. According to these results, further studies are warranted to investigate whether Mesalazine would be an effective treatment for IBS patients, and further studies should be done to account for if Mesalazine has an effect on improving the symptoms of IBS over a longer period of time or to study the effects of the drug on different symptoms of IBS.

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